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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000011	05.01.2004	06.01.2003

International Patent Classification (IPC) or both national classification and IPC
A61K47/48, A61P25/00

Applicant
TRANSFERT PLUS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/000011

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5,7-22,24-39,41-54,56-68,70-78,80-102 partially; 6,23,40,55,69,79 complete

because:

☒ the said international application, or the said claims Nos. 91-102 in relation to industrial applicability, see separate sheet relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-5,7-22,24-39,41-54,56-68,70-78,80-102 partially; see separate sheet are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-4, 7-21,24-38,41-53,56-67,70-78,80-102 partially; 6,23,40,55,69 and 79 complete; see separate sheet

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2004/000011

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 5, 22, 39, 54, 68 complete; 1-4, 7-21, 24-38, 41-53, 56-67, 70-78, 80-102 partially

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,22,39,45,52,58,66,68
	No:	Claims	1-4,7-21,24-38,41-44,46-51,53,56,57,59-65,67,70-78,80-102
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-5,7-22,24-39,41-54,56-68,70-78,80-102
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 91-102 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT.

Claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102 as far as related to the first invention encompass a genus of compounds defined only by their function, namely "carrier able to cross the blood brain barrier after attachment to said agent.." (claims 1, 18); "transporting does not affect blood brain barrier integrity" (claims 2, 19, 36, 51, 65, 77); "transporting effected by receptor mediated transcytosis or adsorptive mediated transcytosis" (claims 8, 25, 42, 57, 71, 81); "agent is releasable form said carrier after transport across the blood brain barrier" (claims 13, 30, 47, 61, 73, 86); "agent is released form said carrier after transport across the blood brain barrier" (claims 14, 31, 48, 62, 74, 87), wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed.

It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Therefore, claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Moreover present claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102 relate to compounds defined by reference to vague characteristics, namely: "a functional derivative" (claims 3, 20, 37, 52, 66, 78); "a drug", "a medicine", "an anticancer agent", "a molecule active at the level of the central nervous system" (claims 4, 21, 38, 53, 67, 76); "agent has a maximum molecular weight of 160,000 Daltons" (claims 7, 24, 41, 56, 70, 80) "a carrier", "an agent attached to said carrier" (claims 18, 35, 50, 64, 76).

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

Furthermore claims 18-22, 24-34, 76-78, 80-102 are not supported by the description (Art. 5 PCT). No support is to be found throughout the application document as filed disclosing the claimed conjugates wherein the agent is an anti-cancer agent, in particular paclitaxel neither the use of the said conjugates as claimed.

The only effective disclosure showing conjugates (description pages 27-30) describe 125I-aprotinin and aprotinin-biotin conjugates not encompassed under the said denomination of anticancer agent conjugate as claimed.

A mere generic enumeration of anticancer agent and not the particular paclitaxel as part of the therapeutic agent is done regardless of its forming part of a conjugate construct (page 15, paragraph 2) and therefore cannot be considered as sufficient disclosure for the skilled person in order to perform the invention in its whole scope (Ar. 5 PCT).

Support with regard to the first invention is only to be found in the present application for those parts relating to the compounds explicitly disclosed in the examples and those specifically mentioned by chemical name in claims 3, 20, 37, 39, 52, 54, 66, 68, 78.

The International Preliminary Examination Authority fully agrees with these objections, therefore no international Preliminary Examination will be carried out in respect of

subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item IV
Lack of unity of invention

The Examining Division agrees with the objection put forward by the Search Division as to lack of unity (Rule 13 PCT), the reasons for the objection being as follows:

The problem underlying the present application is the delivery of drugs across the blood-brain barrier for treating disorders of the central nervous system (see page 1, second paragraph).

As solution to this problem several compositions comprising a carrier and an agent attached thereto with different and very diverse chemical and structural characteristics, among which no homology, activity or functional relationship can be inferred, are proposed.

The common feature linking the different inventions together could therefore only be regarded as the use of a carrier (particularly a polypeptide molecule) for the transport of an agent across the blood-brain barrier.

Prior art documents

DE 19953696 discloses Beta-amyloid A4 (homologue of claimed Angio-pep1 according to present application figure 17; description page 32-33) linked to a synzyme. Optionally conjugated to another molecule (see claim 3, fig. 1). The construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32).

Martel C. L. et al in Pharma Sciences (1997), vol. 7, pp. 28-36 disclose the transport of apolipoprotein J bound to soluble amyloid beta 1-40 (homologue to claimed Angio-pep1 according to present application figure 17, description pages 32-33) across the blood brain barrier (see abstract; page 33, col. 2).

Shimura T. et al in Journal of pharmacology and experimental therapeutics (1991), vol. 258, pp. 459-465 discloses that radiolabelled (5-125I-His) ebiratide (adrenocorticotropic

hormone analog) is transported through the blood-brain barrier via basic peptide specific absorptive mediated endocytosis (see abstract, fig 1).

Demeule M. et al in Journal of Neurochemistry (2002) vol. 83, pp. 924-933 describes that P97 (melanotransferrin) could be advantageously employed as delivery system to target drugs, peptides or enzymes directly to the brain (see abstract, discussion).

The common feature mentioned above is consequently not novel and therefore cannot be regarded as linking the inventions together so as to form a single general inventive concept.

As there is no other technical feature which could fulfil the role of special technical feature in the sense of rule 13.2 PCT, the present application lacks unity of invention, containing the following subjects:

1. Claims: 5, 22, 39, 54, 68 complete; 1-4, 7-21, 24-38, 41-53, 56-67, 70-78, 80-102 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is anticancer agent paclitaxel. Conjugate comprising the carrier and paclitaxel, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity).

2. Claims: 1-4, 6-21, 23-38, 40-53, 55-67, 69-79, 80-102 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is a radioactive label. Conjugate comprising the carrier and radioactive label, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

3. Claims: 1-4, 6-21, 23-38, 40-53, 55-67, 69-79, 80-102 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein

the agent is a green fluorescent protein, a histag protein, and beta galactosidase. Conjugate comprising the carrier and the protein agent, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 91-102 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Reference is made to the following documents:

D1: DE 199 53 696 A (CHERKASKY ALEXANDER) 10 May 2001

D2: SHIMURA T ET AL: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 258, no. 2, 1991, pages 459-465.

D3: DEMEULE M ET AL: JOURNAL OF NEUROCHEMISTRY, vol. 83, no. 4, November 2002, pages 924-933.

D4: SEIDEL G ET AL: NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, vol. 284, no. 4, 1974, page R73.

D5: MARTEL ET AL: STP PHARMA SCIENCES, PARIS, FR, vol. 7, no. 1, 1997,

pages 28-36.

Novelty Article 33(2) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4, 7-21, 24-38, 41-44, 46-51, 53, 56, 57, 59-65, 67, 70-78, 80-102 is not new in the sense of Article 33(2) PCT.

D1 discloses Beta-amyloid A4 (homologue of claimed Angio-pep1 according to present application figure 17; description page 32-33) linked to a synzyme. Optionally conjugated to another molecule (see claim 3, fig. 1). The construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32).
Consequently the subject matter of claims 1-4, 7-21, 24-38, 41, 42, 46-49, 63, 76-78, 80-91, 94 is not new over D1.

D2 discloses that radiolabelled (5-125I-His) ebiratide (adrenocorticotropic hormone analog) is transported through the blood-brain barrier via basic peptide specific absorptive mediated endocytosis (see abstract, fig 1). The conjugate encompasses a construct R-L-M as claimed wherein "L" is the chemical bond attaching 125I to ebiratide.
The treatment of Alzheimer (encompassed under the claimed neurological diseases of present claims 10, 27, 44, 58, 83) is also described (see abstract)
Therefore the subject matter of present claims 1, 2, 4, 7-19, 21, 24-36, 38, 41-44, 46-51, 53, 56, 57, 59-65, 67, 70-77, 80-102 is not novel over D2

Inventive step Article 33(3) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102. does not involve an inventive step in the sense of Article 33(3) PCT.

The problem underlying the present application is the delivery of drugs across the blood-brain barrier for treating disorders of the central nervous system (see page 1, second paragraph).

As solution to this problem a composition comprising a carrier wherein aprotinin and Angio-pep1 are preferred linked to an anticancer agent, in particular paclitaxel is proposed as the first invention.

Previously discussed document D3, which can be considered the closest prior art, already addresses the problem of delivery of drugs across the blood brain barrier with the use of P97 (melanotransferrin) as delivery system to target drugs, peptides or enzymes directly to the brain (see abstract, discussion).

The difference between D3 and the subject matter of present claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102 is the fact that the particular conjugate of aprotinin or Angio-pep1 with an anticancer agent (as paclitaxel) neither the use for the specific treatment of neurological diseases consisting on brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer, Parkinson, Huntington, stroke, blood brain barrier related malfunction disease, obesity are explicitly disclosed in D3.

Nevertheless, D1 renders obvious the use of a beta-amyloid A4 homologue (as the claimed Angio-pep1) conjugated to another molecule as such construct is capable for crossing the blood brain barrier (see col. 1 lines 15-32; claim 3).

The use of aprotinin is also rendered obvious to the skilled person in view of the teaching of D4, where the effect of trasylol (namely aprotinin) in increasing the brain concentration of drug harmine by affecting on the permeability of the blood brain barrier in relation to lymphostatic encephalopathy is described (see abstract).

Furthermore the attention of the applicant is drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step. When the inventive step is solely based on the achievement of a technical effect, such as "transporting of an agent across the blood brain barrier", substantially all embodiments of independent claim 1 should exhibit this effect.

It should be credible that all the alternatives encompassed by the claims are a solution to the problem.

However, it is evident that the number of compounds encompassed under: "carrier able

to cross the blood brain barrier after attachment to said agent.." (claims 1, 18); "agent is releasable form said carrier after transport across the blood brain barrier" (claims 13, 30, 47, 61, 73, 86); "agent is released form said carrier after transport across the blood brain barrier" (claims 14, 31, 48, 62, 74, 87); "a functional derivative" (claims 3, 20, 37, 52, 66, 78); "a drug", "a medicine", "an anticancer agent", "a molecule active at the level of the central nervous system" (claims 4, 21, 38, 53, 67, 76); "agent has a maximum molecular weight of 160,000 Daltons" (claims 7, 24, 41, 56, 70, 80)
is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102 is unlikely to exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03009815	06/02/2003	25/07/2002	25/07/2001

This earlier application shows:
LRP (low density lipoprotein related) receptor ligands including aprotinin and P97 with functional effect on transcytosis (see page 4; fig 17; claim 25) . Conjugates of the same with therapeutic active agents including paclitaxel (see page 37, line 8).
Uses of the same for the treatment of neurological disorders are also described (see claim 8).

Thus, it would be prejudicial to the novelty of the subject-matter of claims 1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102 of the present application.